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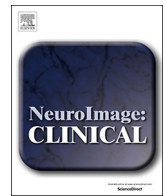


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Altered resting-state functional connectivity in children and adolescents born very preterm short title

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ABSTRACT

The formation of resting-state functional networks in infancy has been reported to be strongly impacted by very preterm birth. Studies in childhood and adolescence have largely focused on language processing networks and identified both decreased and increased functional connectivity. It is unclear, however, whether functional connectivity strength is altered globally in children and adolescents born very preterm and whether these alterations are related to the frequently occurring cognitive deficits. Here, resting-state functional MRI was assessed in a group of 32 school-aged children and adolescents born very preterm with normal intellectual and motor abilities and 39 healthy term-born peers. Functional connectivity within and between a comprehensive set of well-established resting-state networks was compared between the groups. IQ and executive function abilities were tested with standardized tasks and potential associations with connectivity strength were explored. Functional connectivity was weaker in the very preterm compared to the term-born group between the sensorimotor network and the visual and dorsal attention network, within the sensorimotor network and within the central executive network. In contrast, functional connectivity was stronger in the very preterm group between the sensorimotor network and parts of the salience and the central executive network. Little evidence was found that these alterations underlie lower IQ or poorer executive function abilities. This study provides evidence for a long-lasting impact of very preterm birth on the organization of resting-state networks. The potential consequence of these alterations for other neurodevelopmental domains than the ones investigated in the current study warrants further investigation.

1. Introduction

Resting-state functional magnetic resonance imaging (rsfMRI) investigates the temporal correlation of low frequency (< 0.1 Hz) fluctuations in blood oxygen level dependent (BOLD) signal across the brain in the absence of goal directed activity and stimulation (e.g., Fox and Raichle, 2007). Accordingly, rsfMRI allows the identification of intrinsic functional brain networks, so-called resting-state networks (RSNs) - networks with synchronous, spontaneous neuronal activity (Van Dijk et al., 2010). RSNs of both primary (i.e., sensorimotor,

auditory and visual processing network) and higher-order functions, including language, memory, attention and executive functioning, have been identified throughout the brain in adults (Damoiseaux et al., 2006; Fox and Raichle, 2007; Smith et al., 2009). Across childhood and adolescence, continuous refinement processes of RSNs have been reported (Fair et al., 2008; Fair et al., 2009; Fair et al., 2007) and maturational trajectories of RSNs were shown to not only mimic the pattern of structural brain development (i.e., myelination and synaptogenesis) but also to parallel the maturational sequence of cognitive and behavioural ability acquisition (Gao et al., 2014).

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Various studies have investigated the impact of very preterm birth (i.e., birth before 32 weeks of gestation) on intrinsic brain networks: At term-equivalent age, a similar set of RSNs as apparent in term-born infants was identified in very preterm infants (Doria et al., 2010), however, weaker functional connectivity across many of these brain networks was reported (Gozdas et al., 2018; Kwon et al., 2014; Kwon et al., 2015; Smyser et al., 2010). Further, very preterm infants with moderate to severe white matter injuries were found to show greater loss of connectivity than very preterm infants without white matter injuries and term-born infants (Smyser et al., 2013). Reductions in functional connectivity between RSNs have been reported to persist into early childhood (Damaraju et al., 2010) and were also found in young adults born very preterm (White et al., 2014).

In children and adolescents born very preterm, previous studies on functional connectivity have largely focused on networks involved in language processing: They reported profound alterations in functional connectivity in very preterm compared to term-born children and adolescents within and between language areas as well as between language areas and other parts of the brain, e.g., the frontal lobe (Gozzo et al., 2009; Myers et al., 2010; Scheinost et al., 2014; Wilke et al., 2014). Importantly, the reported alterations in the functional organization of language networks have been found to be related to poorer verbal abilities (Myers et al., 2010; Scheinost et al., 2014; Wilke et al., 2014). Thus, assessing the functional connectivity of the resting brain may provide valuable insight into underlying mechanisms of impaired cognitive development after very preterm birth.

So far, it is unknown how functional brain networks other than those involved in language processing are affected by prematurity in children and adolescents. The pattern of neurodevelopmental deficits evident in this population is complex (Latal, 2009) and commonly includes lower general cognitive abilities (i.e., IQ) and poorer executive functions (see e.g., Brydges et al., 2018 for a meta-analysis). To advance the current understanding of unfavourable outcome after very preterm birth, a better understanding of the underlying neuronal mechanisms is needed, yet, studies investigating global functional network connectivity alterations and potential associations with neurodevelopmental deficits are currently lacking.

Hence, in the current study (i) the functional connectivity within and between well-established RSNs (i.e., default mode network (DMN), salience network (SN), dorsal attention network (DAN), sensorimotor network (SMN), visual network (VN), language network (LN), central executive network (CEN) and cerebellar network (CN), Damoiseaux et al., 2006) is compared between school-aged children and adolescents born very preterm and their term-born peers and (ii) associations between connectivity strength within and between these networks and cognitive abilities (IQ and executive functions) are explored.

2. Material and methods

2.1. Participants and study procedure

The inclusion criteria and selection process for the study have been described in detail previously (Wehrle et al., 2016; Wehrle et al., 2017). In short, very preterm participants were included if they fulfilled the following criteria: birth ≤ 32 weeks of gestation, no major brain injuries seen on neonatal ultrasound (i.e., severe white matter injuries, such as porencephalic cysts or cystic periventricular leukomalacia, any intraventricular hemorrhage $>$ grade II), normal intellectual and motor development at the age of five years and aged between 10 and 16 years at the time of the current study. Forty-one children and adolescents born very preterm agreed to participate. Additionally, 43 typically-developing siblings and friends of the very preterm participants and children and adolescents recruited from local schools were included in the control group. MR imaging was performed at the Center for MR Research following a session of neurodevelopmental testing at the Child Development Center, both at the University Children's Hospital Zurich,

Switzerland. All assessments were completed between January and December 2013. The study was approved by the local ethical committee. Written informed consent was obtained from a parent and from participants older than 15 years. Younger participants provided oral consent. Participants were compensated with a gift certificate.

For very preterm participants, perinatal data was derived from medical records. In all participants, socio-economic status (SES) was estimated with a 6-point scale based on paternal occupation and maternal education (Largo et al., 1989).

2.2. MR imaging

2.2.1. Image acquisition

Magnetic resonance imaging (MRI) was performed on a 3 T GE MR750 whole-body system using an 8 channel receive-only head coil. Possible head movements were minimized by placing foam pads inside the head coil and instructing the participants to remain still throughout the scanning session. Hearing was protected with earplugs and MR-compatible headphones. Anatomical images of the entire brain were obtained for all participants with a high-resolution three-dimensional T1-weighted spoiled gradient-recalled echo sequence (time of repetition = 11 ms, time of echo = 5 ms, inversion time: 600 ms, flip angle: 8°, resolution: 1 mm isotropic). All images were anatomically evaluated by a neuroradiologist. RsfMRI was acquired with an echo-planar imaging sequence (time of repetition: 1.925 s, time of echo: 32 ms, in plane voxel resolution: $3.75 \times 3.75 \text{ mm}^2$, field of view: $240 \text{ mm} \times 240 \text{ mm}$, duration: 6.19 min, slice thickness: 3 mm). During the rsfMRI sequence, participants were instructed to keep their eyes open and fixate on a black cross presented on a white screen, viewed via a mirror.

2.2.2. Functional network connectivity analyses

RsfMRI was analyzed using the CONN toolbox, version 17e (Whitfield-Gabrieli and Nieto-Castanon, 2012). Data were band-pass filtered (0.01–0.1 Hz). The following post-processing steps were performed: Realignment (head motion correction), outlier scrubbing (Power et al., 2012), functional and structural segmentation, normalization (MNI space normalization), and outlier detection (using ARTifact detection Tools) as well as spatial smoothing (6 mm). CONN accounts for bad data points (using the 'ART detection' toolbox) by including bad data point and movement time courses as nuisance regressors during the denoising procedure. Thus, data is not being inserted or interpolated with CONN. In addition to the six motion parameters, white matter and cerebrospinal fluid signals were used as covariates of no interest to reduce variance unlikely to reflect functional connectivity-related neuronal activity. Only the white matter and cerebrospinal fluid signals were removed to avoid any bias introduced by removing the global signal (i.e., grey matter). This denoising step has been shown to 'normalize' the distribution of voxel-to-voxel connectivity values as effectively as including the global signal as a covariate of no interest but without the potential problems of the latter method (Behzadi et al., 2007; Murphy et al., 2009). Additionally, linear detrending was performed during the denoising step. After the denoising step, the distribution of voxel-to-voxel connectivity was visualized for each step. All participants showed normally distributed data after denoising and were therefore included into further analyses.

Between-group differences in functional connectivity were assessed on the network level (functional network connectivity, FNC). Connectivity strength between the seeds (indicated in brackets) of the following eight well-established RSNs were compared between groups: DMN (middle prefrontal cortex (mPFC), bilateral lateral parietal cortex (IPC), posterior cingulate cortex (PCC)), SN (anterior cingulate cortex (ACC), bilateral anterior insula cortex (AI), bilateral rostral prefrontal cortex (rPFC), supramarginal gyrus (SMG)), DAN (bilateral frontal eye field (FEF), bilateral intraparietal sulcus (IPS)), SMN (bilateral lateral and superior sensorimotor regions), VN (primary, ventral and bilateral dorsal visual cortex), LN (inferior frontal gyrus (IFG), posterior superior

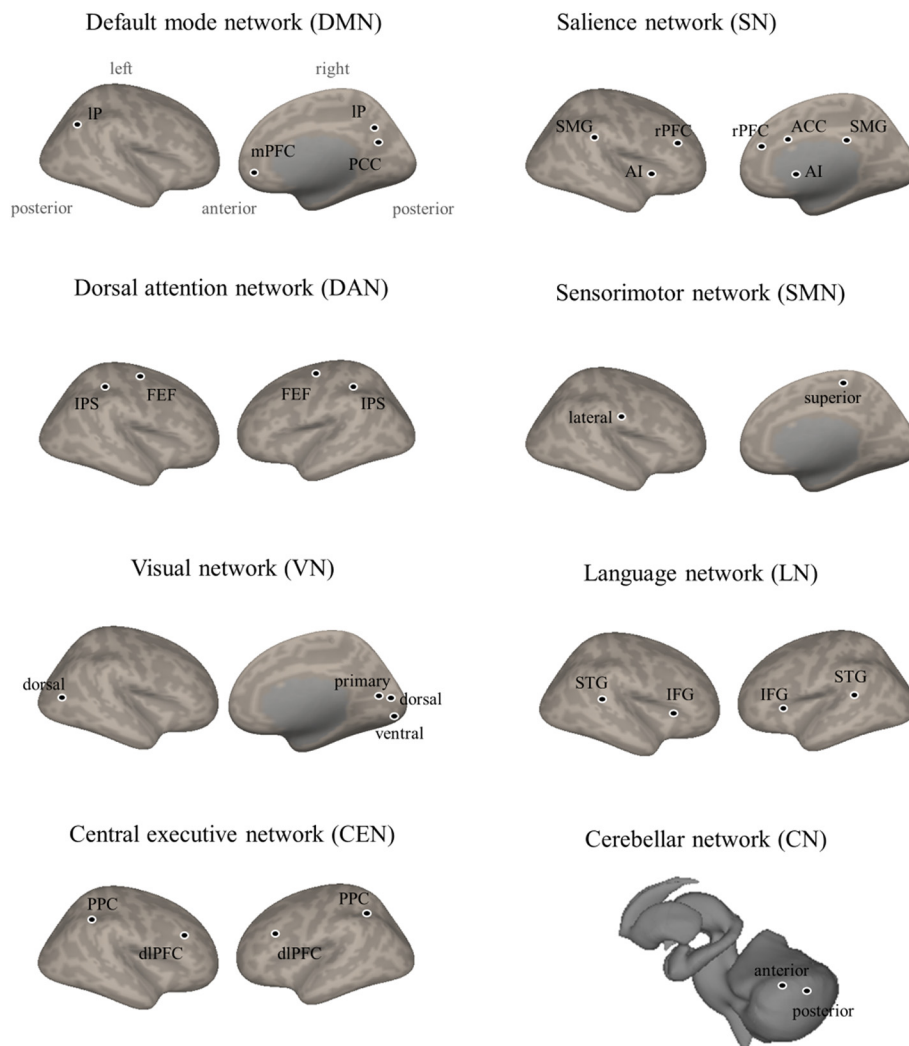


Fig. 1. Illustration of the eight resting-state networks and their respective seeds. For anatomical structures with MNI coordinates of $x = 0$, medial instead of lateral views are shown (i.e., DMN, SN, SMN and VN). ACC: anterior cingulate cortex, AI: anterior insula cortex, dlPFC: dorsolateral prefrontal cortex, FEF: frontal eye field, IFG: inferior frontal gyrus, IPS: intraparietal sulcus, IPC: lateral parietal cortex, mPFC: middle prefrontal cortex, PCC: posterior cingulate cortex, PPC: posterior parietal cortex, rPFC: rostral prefrontal cortex, SMG: supramarginal gyrus, STG: superior temporal gyrus.

temporal gyrus (STG)), CEN (bilateral dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC)) and CN (anterior and posterior cerebellum). The eight networks are depicted in Fig. 1. For each ROI, the time-series of interest is defined as the average BOLD activation within the ROI voxels (CONN default). Connectivity strength values were extracted for connections with significant group differences in FNC.

2.3. Neurodevelopmental assessment

The neurodevelopmental test battery administered in this study has been described in detail previously (Wehrle et al., 2016). In short, to estimate IQ, an abbreviated version of the Wechsler Intelligence Scale for Children (WISC-IV; German version, Petermann and Petermann, 2006), including the subtests ‘Block design’, ‘Vocabulary’, ‘Letter-number-sequencing’ and ‘Symbol Search’ was used. This subtest combination has been shown to correlate with the full version ($r = 0.95$; Waldmann, 2008). To assess fine motor abilities, the pegboard task of the Zurich Neuromotor Assessment (Largo et al., 2007) was applied in a subgroup of participants (26 very preterm and 29 term-born participants). Executive function abilities were assessed with four tasks: Spatial working memory, cognitive flexibility and planning were assessed with subtests of the Cambridge Neuropsychological Test Automated

Battery (CANTAB; Cambridge Cognition Ltd., 2004) and verbal fluency was assessed with the Regensburger Wortflüssigkeitstest, a German-language verbal fluency task (Aschenbrenner et al., 2000). To obtain equal scaling between the tasks, the total score of each task was z-transformed using the mean and standard deviation of the control group. The four resulting z-scores were averaged to reflect overall executive function abilities.

2.4. Statistical analysis

For the FNC analyses, group differences were investigated by regression analyses. Birth status (very preterm vs. term) was defined as independent variable while the respective network connections were defined as dependent variables. Sex and age at assessment were defined as covariates of no interest. T-values were calculated as $t = b1/SE$ (with $b1$ = slope of the sample regression line, SE = standard error of the slope). Results are reported at $p \leq .05$ (FDR seed-level correction, two-sided). Demographic and neurodevelopmental outcome measures were compared between groups using Chi square test, independent Student's *t*-test and univariate analyses of covariance (ANCOVA, controlling for SES) as appropriate. The associations between connectivity strength and cognitive abilities (i.e., estimated IQ and the executive function composite score) were investigated while correcting for sex and age at

assessment (step 1) and for sex, age at assessment and birth status (step 2) using partial correlation. The significance level was set to $p \leq .05$. (two-tailed, uncorrected). Statistical analyses were performed in R (Chang, 2014; R Core Team, 2015; R Core Team, 2016; Revelle, 2017; Seongho, 2015; Wickham, 2016).

3. Results

3.1. Sample description and neurodevelopmental assessment

One very preterm participant refused MR scanning at the day of testing. Data of 11 participants (7 very preterm and 4 term-born participants) was excluded due to imaging artifacts (e.g., translational head motion > 1 mm). One very preterm participant was excluded for further analyses due to an arachnoid cyst and subsequent left cerebellar hypoplasia. Therefore, the final sample consisted of 32 very preterm and 39 term-born children and adolescents.

Mean gestational age of the very preterm participants was 29.6 (SD: ± 2.0 ; range: 25.1–32.0) weeks and mean birthweight was 1256 (± 343 ; 840–1990) g. All term-born participants were born after 37 weeks of gestation and with a birth weight of > 2500 g (for detailed perinatal data see Supplementary Table 1). Demographic, socio-economic and neurodevelopmental data of the two groups is presented in Table 1.

3.2. Functional network connectivity differences

Mean head motion was not significantly different between the very preterm ($x = -0.009$ (0.14; -0.37 to 0.18), $y = 0.11$ (0.33; -0.37 to 1.7) and $z = 0.13$ (0.38; -0.37 to 1.32)) and the term-born group ($x = 0.03$ (0.09; -0.22 to 0.2), $y = 0.09$ (0.14; -0.19 to 0.41) and $z = 0.0009$ (0.4; -0.62 to 1.5), $p = .15$, 0.77 and 0.16 , respectively). Further, the number of detected bad data points was not significantly different between the groups (very preterm group: 5.4 (9.9; 0–37); term-born group: 2.3 (4.3; 0–21), $p = .08$).

Fig. 2 illustrates FNC differences between the very preterm and term-born group (controlling for sex and age at assessment). Very preterm participants showed significantly stronger connectivity compared to term-born participants between the following RSNs: The SMN (left and right lateral sensorimotor regions) and two regions of the SN (left rPFC and left ACC) and between the SMN (left lateral sensorimotor

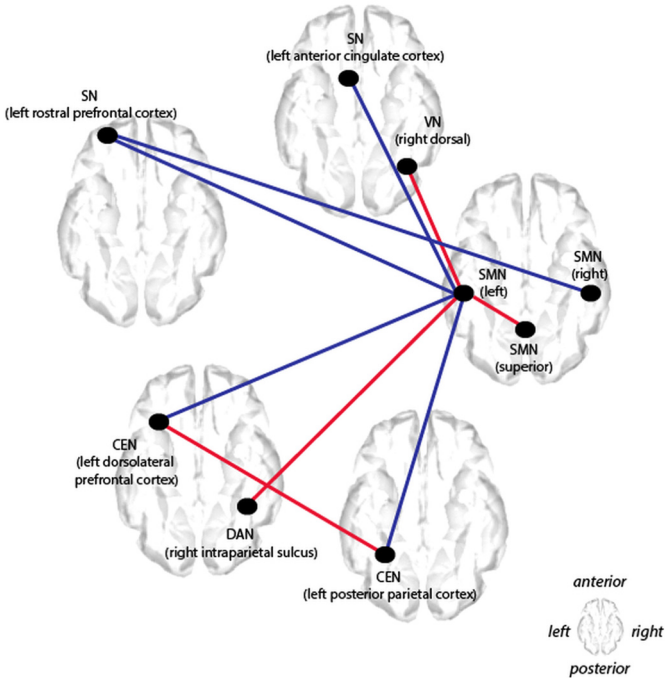


Fig. 2. Significant group differences in functional network connectivity (FNC) between very preterm and term-born children and adolescents at school age. Blue lines indicate connections with stronger connectivity strength in the very preterm group, red lines indicate connections with weaker connectivity strength in the very preterm group compared to the term-born group. $p < .05$ FDR corrected.

regions) and two regions of the CEN (left PFC and PPC). Very preterm participants showed weaker connectivity between the SMN (left lateral sensorimotor regions) and the VN (right dorsal visual cortex), the SMN (left lateral sensorimotor regions) and the DAN (right IPS), within the CEN (left dlPFC and left PPC) and within the SMN (left lateral and superior sensorimotor regions). The corresponding t -values are reported in Table 2.

3.3. Association between connectivity strength and cognitive abilities

The correlations between the connectivity strength of the RSNs with significantly different FNC in very preterm and term-born participants (as depicted in Fig. 2 and listed in Table 2A) and cognitive abilities are shown in Table 2B and C. Across all participants, connectivity strength between the SMN (left and right lateral sensorimotor regions) and the SN (left rPFC) and between the SMN (left lateral sensorimotor regions) and the SN (left ACC) was negatively related to estimated IQ ($r = -0.32$, $p = .007$, $r = -0.29$, $p = .01$ and $r = -0.33$, $p = .005$, respectively). The executive function composite score was negatively related to connectivity strength between the SMN (left lateral sensorimotor regions) and the SN (left dlPFC) ($r = -0.28$, $p = .02$ and $r = -0.27$, $p = .03$, respectively). Additionally controlling for birth status reduced these associations to non-significant with only two associations remaining marginally significant (namely, the associations between estimated IQ and the connectivity strength between the SMN (left lateral sensorimotor regions) and two regions in the SN (left rPFC, $p = .06$ and left ACC, $p = .07$). Fig. 3A and B illustrate these associations.

4. Discussion

In this study, the strength of the functional connectivity within and between well-established intrinsic brain networks assessed at rest (i.e.,

Table 1 Demographic, socio-economic and neurodevelopmental data.			
	Very preterm group	Term-born group	
Demographic and socio-economic data	($n = 32$)	($n = 39$)	p
Age at assessment, M (SD), range (in years)	12.8 (1.6) 10.4–16.6	13.0 (2.1), 10.0–16.6	0.51
Sex distribution (n)	19 boys/13 girls	20 boys/19 girls	0.66
Socio-economic status M (SD), range ^a	4.9 (1.7; 2–8)	4.0 (1.7; 2–8)	0.03
Neurodevelopmental data, M (SD), range			p^b
Estimated IQ	104.2 (7.0), 91–118	109.4 (6.7), 99–129	0.02
Fine motor abilities (in seconds)	22.7 (4.7), 17.2–37.4	22.1 (3.6), 15.5–29.7	0.27
Executive function abilities (z-score)	−0.60 (0.8), −2.5–0.06	0.04 (0.8), −2.0–1.1	0.02

^a Scale from 1 to 12; higher values indicating lower socio-economic status (SES).
^b Corrected for SES.

Table 2
A–C Significant group difference in functional network connectivity (FNC) between very preterm and term-born groups (A) and associations between connectivity strength and estimated IQ (B) and executive function abilities (C).

	A Group difference in connectivity strength			B Association with estimated IQ			C Association with executive function composite score		
	t	p ^a	r ^b	p ^b	r ^c	p ^c	p ^b	r ^c	p ^c
FNC stronger in very preterm vs. term-born group									
SMN (left lateral sensorimotor regions) – SN (left rPPC)	–2.89	0.027	–0.32	0.007	–0.23	0.06	–0.17	0.15	–0.06
SMN (right lateral sensorimotor regions) – SN (left rPPC)	–3.46	0.029	–0.29	0.01	–0.15	0.21	–0.15	0.21	0.01
SMN (left lateral sensorimotor regions) – SN (left ACC)	–3.52	0.012	–0.33	0.005	–0.22	0.07	–0.28	0.02	–0.17
SMN (left lateral sensorimotor regions) – CEN (left dIPFC)	–3.62	0.012	–0.22	0.08	–0.08	0.51	–0.27	0.03	–0.15
SMN (left lateral sensorimotor regions) – CEN (left PPC)	–3.28	0.017	–0.14	0.24	–0.01	0.94	–0.18	0.14	–0.06
FNC weaker in very preterm vs. term-born group									
SMN (left lateral sensorimotor regions) – VN (right dorsal visual cortex)	2.83	0.028	0.15	0.23	0.03	0.79	0.06	0.62	–0.06
SMN (left lateral sensorimotor regions) – DAN (right IPS)	2.99	0.024	0.17	0.16	0.06	0.64	0.17	0.16	0.06
CEN (left dIPFC) – CEN (left PPC)	3.33	0.022	0.17	0.16	0.04	0.75	0.19	0.12	0.07
SMN (left lateral sensorimotor regions) – SMN (superior sensorimotor regions)	3.02	0.024	0.09	0.49	–0.04	0.74	0.13	0.27	0.02

ACC: anterior cingulate cortex, CEN: Central executive network, dIPFC: dorsolateral prefrontal cortex, FNC: Functional network connectivity, IPS: Intraparietal sulcus, PPC: Posterior parietal cortex, rPPC: rostral prefrontal cortex, SMN: Sensorimotor network. Significant correlations (incl. marginal significance, i.e., $p \leq .10$) between connectivity strength and cognitive abilities are indicated in bold.

^a FDR-corrected p -values.

^b Corrected for sex and age at assessment.

^c Corrected for sex age at assessment and birth status.

RSNs) was compared between school-aged children and adolescents born very preterm and typically-developing term-born peers. A pattern of both increased and decreased connectivity strength was found in the very preterm group, particularly between RSNs of sensorimotor areas and those involved in higher-order cognitive functions, namely the salience, central executive and dorsal attention networks. Little evidence was found that these alterations in the functional organization of the preterm brain are related to lower estimated IQ or poorer executive function abilities.

Previously, studies investigating functional connectivity in very preterm children and adolescents have mainly focused on brain networks involved in language processing: Connectivity strength was assessed either while the children performed a language task or at rest and both reductions and increases in very preterm children and adolescents compared to term-born peers have been reported (see [Kwon et al., 2016](#) for a review). In contrast to focusing on specific functional brain networks, in the current study, within- and between-network connectivity strength was investigated in a comprehensive set of well-established intrinsic brain networks, namely the DMN, the SN, the DAN, the SMN, the VN, the LN, the CEN and the CN ([Damoiseaux et al., 2006](#)). The findings of the current study provide evidence for long-lasting and widespread alterations of FNC in children and adolescents born very preterm, affecting a range of RSNs involved in visual, sensorimotor and higher-order cognitive processing, namely the VN, the SMN, the SN, the CEN and the DAN. These widespread differences between very preterm and term-born children and adolescents are partly in line with previous studies of adults born very preterm. For example, [Finke et al. \(2015\)](#) reported altered functional connectivity in parts of the VN and DAN in 26-year old former preterm patients when focusing on networks involved in visual selective attention processes ([Finke et al., 2015](#)). Also, prominent alterations in parts of the SN have been reported in very preterm adults at age 28 years when investigating the CEN, SN and DMN ([White et al., 2014](#)). In the current study, no FNC differences between very preterm and term-born children and adolescents were identified in language networks. This is in contrast to previous studies (as discussed above), however, direct comparisons are difficult to draw as previous studies have mostly assessed functional connectivity during the performance of a language task (see [Kwon et al., 2016](#) for an overview) and not during rest. Importantly, the findings of the current study show that alterations in FNC may not be restricted to language processing areas but that preterm birth may have a rather global impact on the functional organization of the brain even when assessed during rest.

In the current study, co-occurring patterns of increased and decreased FNC in very preterm individuals compared to term-born peers were identified. Specifically, stronger connectivity in the very preterm group was identified between the SMN and both the SN and the CEN. In parallel, weaker connectivity was identified between the SMN and both the VN and the DAN, within the SMN and within the CEN. Similarly, in previous studies, both increased and decreased functional connectivity was reported in the preterm population: A study in very preterm adults found decreased connectivity, particularly in the SN ([White et al., 2014](#)) while several studies in very preterm children and adolescents reported increased functional connectivity within and between language networks ([Myers et al., 2010](#); [Wilke et al., 2014](#)). In line with the current findings, Finke and colleagues, moreover, identified both increased and decreased connectivity in very preterm adults ([Finke et al., 2015](#)). Commonly, decreased connectivity strength has been interpreted as the result of long-lasting detrimental effects of preterm birth on the organization of intrinsic brain network connectivity (e.g., [White et al., 2014](#)). In contrast, the meaning of increased connectivity strength in very preterm individuals has been discussed in various ways, including as an adaption mechanism employed by the brain to cope with early neurologic insult due to preterm birth. Providing support for this interpretation, [Bäumli et al. \(2014\)](#) reported an overlap of regions with increased FNC and decreased grey matter volume in adults

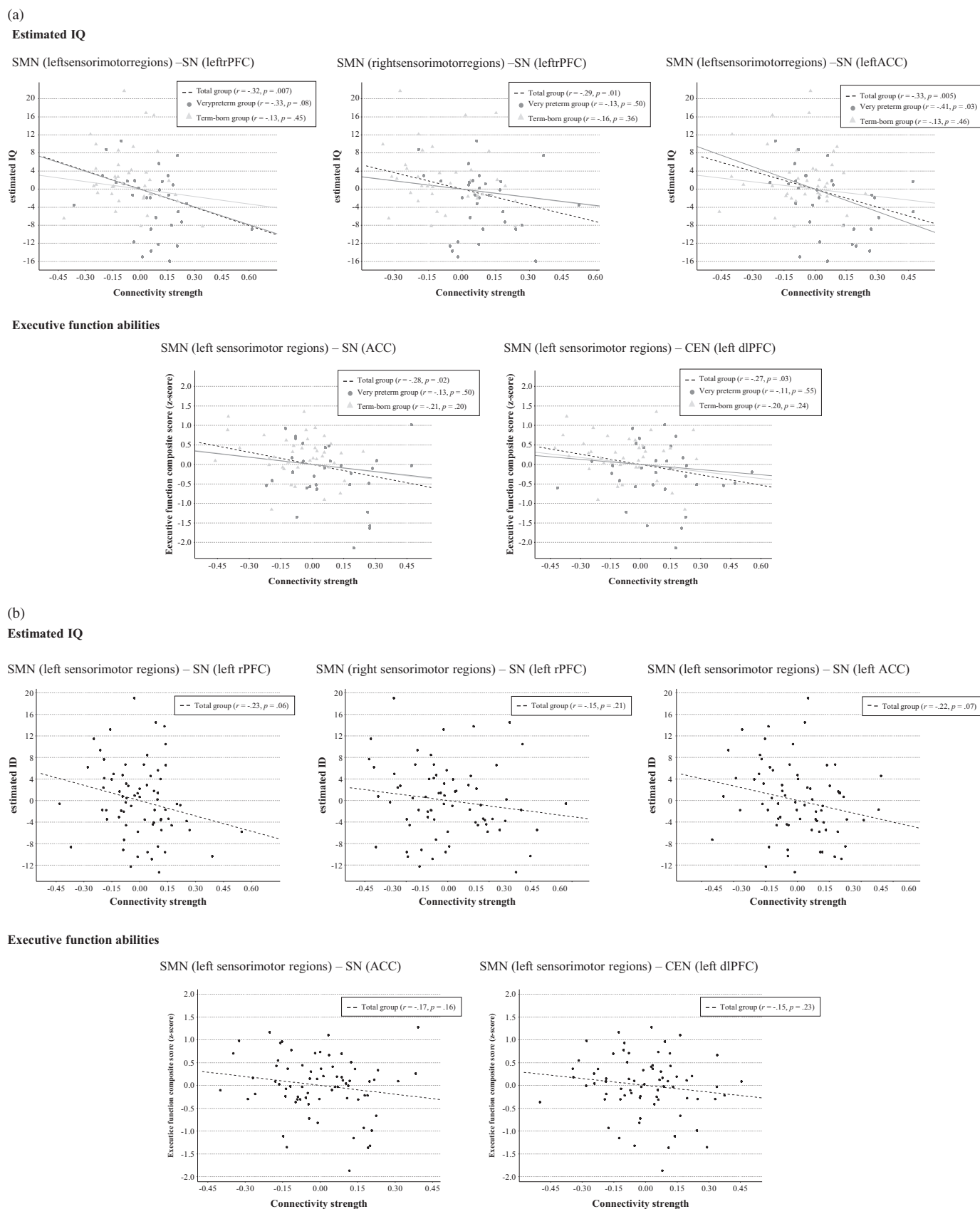


Fig. 3. Partial correlation between connectivity strength and cognitive abilities corrected for sex and age at assessment in very preterm and term-born children and adolescents at school age (A) and corrected for sex, age at assessment and birth status (B). ACC: anterior cingulate cortex, CEN: central executive network, dlPFC: dorsolateral prefrontal cortex, SMN: sensorimotor network, SN: salience network.

born preterm in subcortical and temporal brain areas, with stronger connectivity being directly related to lower grey matter volumes in these regions (Bäumel et al., 2014). Other studies have hypothesized that the increased connectivity strength within and between specific RSNs seen in very preterm individuals may have resulted from a disruption of normal maturation. For example, in a study with late-preterm children aged 9 to 13 years, the ‘hyperconnectivity’ within posterior parts of the DMN, within the CEN and within the SN was suggested to indicate a failure to progress beyond initial rudimentary to more mature distributed networks and, thus, may reflect a disruption of normal synaptic pruning (Degnan et al., 2015a; Degnan et al., 2015b). This interpretation is supported by findings from studies in typically-developing children and adolescents, which reported a continuous refinement of RSNs across childhood and adolescents, including changes of connectivity strength within and between networks (e.g., de Bie et al., 2012; Fair et al., 2008; Fair et al., 2009; Fair et al., 2007; Thornburgh et al., 2017; Van Duijvenvoorde et al., 2016). Ultimately, only longitudinal studies including repeated assessments of RSNs will be able to provide definite answers on the functional meaning of altered functional connectivity in the preterm brain across development. However, in the current study, all group differences between very preterm and term-born participants emerged after the age at assessment was taken into account, thus, providing evidence for alterations in RSNs due to preterm birth which are not dependent on age.

In the current study, the majority of differences in FNC between very preterm and term-born participants involved sensorimotor regions, particularly the lateral SMN. Previously, it has been reported that preterm patients with spastic diplegia show decreased functional connectivity in motor, including sensorimotor, regions, while, at the same time, these connections were found to be expanded to adjacent parietal regions (Lee et al., 2011). Similarly, weaker connectivity between sensorimotor areas and posterior brain areas, specifically the IPS (part of the DAN) and the dorsal visual cortex (part of the VN) were found in the very preterm compared to the term-born group in the current study, even though only children with normal motor abilities (i.e., no signs of cerebral palsy) were included. In parallel to the weaker connectivity between the SMN and posterior brain regions, increased connectivity strength was found between sensorimotor regions and parts of the SN and the CEN in the very preterm compared to the term-born group in the current study. Interestingly, Schafer et al. (2009), reported that functional connectivity between sensorimotor and language areas during a language task was only apparent in preterm but not in term-born children (Schafer et al., 2009). Together with the results of the current study, this may provide evidence that sensorimotor regions play a particularly important role in the functional re-organization of the brain following very preterm birth. Further studies investigating a comprehensive set of RSNs or which specifically focus on the role of the SMN in intrinsic brain network connectivity following preterm birth will shed light on this issue.

Limited evidence was found for a detrimental effect of the reported alterations in functional connectivity strength for neurodevelopmental outcome following very preterm birth: The associations between connectivity strength and cognitive abilities which were apparent across both groups disappeared when birth status was additionally accounted for. Likely, a common cause, namely very preterm birth, underlies both the altered functional organization of the brain and the deficits in cognitive abilities. Thus, future studies need to continue the investigation of the potential mechanisms through which preterm birth leads to neurodevelopmental deficits. While the current study does not provide any strong evidence for a detrimental effect of altered connectivity strength for cognitive abilities, some of the reported associations with estimated IQ remained marginally significant even after taking birth status into account. Namely, stronger functional connectivity between sensorimotor areas and parts of the SN was associated with lower estimated IQ after taking birth status into account. This may suggest an independent contribution of altered functional

connectivity between these networks to the observed differences in estimated IQ. Importantly, the SN has previously been shown to play a pivotal role in general cognitive and executive function abilities (e.g., Hilger et al., 2017; Iannaccone et al., 2015; Sridharan et al., 2008). The involvement of the SMN in cognitive abilities, in contrast, is less well understood. These results need to be interpreted with caution and require replication in future studies before being integrated into the existing body of research on the relevance of altered functional connectivity for neurodevelopmental deficits following preterm birth. Nonetheless, they may add to previous work by highlighting the need to consider networks which may not have been traditionally associated with cognitive abilities, i.e., the SMN, for a comprehensive view on how preterm birth impacts the functional re-organization of intrinsic brain networks and subsequent neurodevelopmental outcome.

4.1. Limitations

While providing new insight into the comprehensive re-organization of intrinsic brain networks in children and adolescents born very preterm, the current study has a number of limitations which need to be considered. First, the sample size of the study was rather small, despite being comparable to other studies investigating functional connectivity in very preterm individuals (e.g., Finke et al., 2015; Myers et al., 2010; White et al., 2014; Wilke et al., 2014). The limited sample size may have restricted the identification of subtle group differences in FNC and group specific associations between connectivity strength and cognitive abilities. Also, it precluded the correction for multiple comparisons when investigating these associations. Further, the assessed study cohort comprised only healthy, well-functioning very preterm individuals as they had not suffered from any major neonatal brain injuries and had shown normal intellectual and motor abilities at age five years. This may have reduced FNC differences between the two groups, thus, making it even more difficult to identify effects. Nonetheless, the study revealed prominent differences in FNC between very preterm and term-born individuals, therefore, reflecting robust alterations of the intrinsic brain network organization due to preterm birth.

Prominent differences in FNC between sensorimotor regions and other intrinsic brain networks, namely the SN, the CEN, the DAN and the VN, were identified in the current study. Traditionally, the SMN is thought to be related to motor abilities (Smith et al., 2009). Unfortunately, no detailed assessment of motor abilities was performed in this study cohort. Merely fine motor abilities were assessed in a subgroup of participants and no difference between the very preterm and term-born group was evident. Possibly, the reported alterations in functional connectivity strength affect other aspects of motor abilities rather than estimated IQ and executive function abilities, the neurodevelopmental domains in the focus of the current study. Future studies should investigate this further.

The cohort assessed in this cross-sectional study covered a relatively wide age-range, including children and adolescents between 10 and 16 years of age. Functional connectivity within and between intrinsic brain networks has been shown to undergo continued refinement processes during this age period (de Bie et al., 2012; Fair et al., 2008; Fair et al., 2009; Fair et al., 2007; Thornburgh et al., 2017; Van Duijvenvoorde et al., 2016). In the current study, the differences in FNC between the very preterm and term-born group emerged after controlling for the age at assessment. While this hints towards a long-lasting effect of preterm birth, it cannot inform about the impact of ongoing maturational processes. To shed light on how altered FNC patterns due to preterm birth develop over time, longitudinal studies with multiple assessment time-points are required in the future.

5. Conclusion

The current study provides evidence for a long-lasting impact of very preterm birth on the organization of intrinsic brain networks.

School-aged children and adolescents born very preterm show a pattern of both increased and decreased functional connectivity strength compared to term-born peers, particularly within and between networks involved in higher-order cognitive functions. Future studies should confirm and continue to investigate how the altered connectivity patterns in children and adolescents born very preterm affects neurodevelopmental outcome.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2018.10.002>.

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